II. Remarks

Status of the Application

Claims 9, 10, 16, 17 and 19-28 are pending. Claims 1-8, 11-15 and 18 are cancelled as being outside the currently elected group. New claims 22-28 are added. Claims 10, 16, 23 and 24 are withdrawn pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species.

Election/Restriction

Applicants acknowledge the telephonic election of the following species: inflammatory lung disease.

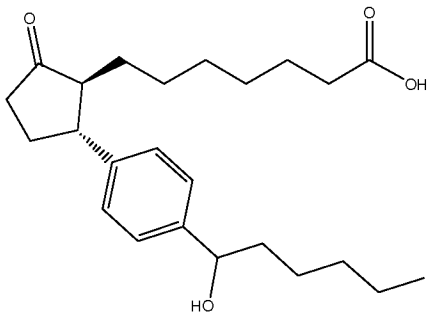
Rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103

Claims 9, 17, and 19-21 were rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 as being anticipated and obvious over Nials et al. (Cardiovascular Drug Reviews, 11(2): 165-179, 1993).

Nials reference

Nials addresses "whether the selective prostanoid EP_2 receptor agonist AH13205 represents a potentially useful class of drug for the treatment of reversible obstructive airways disease" (see first three lines of the discussion section on page 175).

AH13205 is



trans-2[-4-(1-hydroxyhexyl)phenyl]-5-oxocyclo pentaneheptanoic acid

Nials does not mention any of the other 7 enantiomers of 2[-4-(1-hydroxyhexyl)phenyl]-5-oxocyclo pentaneheptanoic acid.

Although the authors saw no evidence of systemic toxicity in rats or dogs and did see pronounced relaxant activity in airway smooth muscle from both guinea pig and cat, they saw no bronchodilator activity in humans (see last paragraph of page 178).

Rejection under 35 U.S.C. § 102

The Examiner describes that "Nials *et al.* teach AH13205 . . . and show its relaxant activity on guinea pig isolated trachea and other EP_2 receptor-containing preparations via prostanoid EP_2 receptor." The examiner further states that the "reference further teaches that AH13205 has smooth muscle relaxant properties and some anti-inflammatory activity.

The examiner recognizes that the reference is silent about the individual stereoisomers of AH13205. The examiner argues however that the racemic mixture inherently contains the RSR and RSS stereoisomers and therefore Nials anticipates the claimed invention "in the absence of any indication in the instant claims that each stereoisomer must be essentially exist in a purified or isolated form".

Claim 9 has been amended to require that the enantiomer is in a purified form. In addition, new claim 22 requires the enantiomer to be substantially pure. The remainder of the pending claims are dependent either from Claim 9 or from claim 22 and thus necessarily include such a limitation.

Applicants submit that amended claim 9 and new claim 22 are not anticipated by the Nials reference. Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 102.

Rejections under 35 U.S.C. § 103

Claims 9, 17, and 19-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nials *et al*. (Cardiovascular Drug Reviews, 11(2): 165-179, 1993).

The examiner states that "Nials *et al.* teach AH13205 . . . in a recemic [sic] mixture can be used for the treatment of inflammatory lung disease". The examiner correctly states that the reference "does not specifically teach individual stereoisomers of AH13205 as claimed in the instant application". The examiner concludes however that it "would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a certain stereoisomer of AH13205 for the treatment of inflammatory lung disease as taught by *Nials et al.* with a with a reasonable expectation of success" because

1) AH13205 is taught to be effective for treating inflammatory lung disease and

2) "the skilled artisan would have expected the stereoisomers to be separable and such separated isomers to exhibit physiological effects similar to those of their racemic mixture" (page 7 of the office action).

Nials does not teach that AH13205 is useful for the treatment of inflammatory lung disease.
On the contrary, Nial teaches that "AH13205 does not appear to have any bronchodilator activity in humans, but does cause marked irritancy in the upper respiratory tract. The authors further state that "[w]e do not intend to conduct any further studies into the potential of AH13205 as a treatment for reversible obstructive airways disease, and indeed the present data suggest no EP_2-receptor agonist is likely to prove effective for such an application." (See the last paragraph on page 178.)

The skilled artisan would not reasonably expect success
The examiner states that "[t]he skilled artisan would have expected stereoisomers to be separable and such separated isomers to exhibit physiological effects similar to those of their racemic mix." (page 7 of the office action).

Based on the examiner's reasoning the stereoisomers would be expected to have no bronchodilator activity in humans and thus the skilled artisan would have a reasonable expectation that the stereoisomers would be ineffective and would be discouraged from expending effort to separate the isomers.

There was no motivation for one of skill in the art to attempt to separate the isomers

As discussed above Nials teaches away from the use of AH13205. In addition, there is no other motivation within Nials to suggest that the stereoisomers be separated. There is nothing within the Nials reference that would suggest to one skilled in the art that separating the isomers would be desirable. The Nials reference does not even discuss the chiral center to which, in part, the present invention relates. Nials does not provide any suggestion that the activity or properties of the compound could be improved by separation of the racemate.

No Prima facie case
The examiner has failed to show that there was reasonable expectation of success or motivation to separate the isomers and therefore has not made a prima facie case of obviousness.

Possession of the racemate does not equal possession of a stereoisomer of the racemate.

The Examiner states that "possessing compounds known to contain chiral centers places all the resultant isomers in the skilled artisan's possession." Applicants strongly disagree with the examiner.

The inventors of the present invention failed many times in their attempts to purify the 4 trans-stereoisomers. "Attempts were carried out on a mixture of all the stereoisomers in their acid form using chiral HPLC using a variety of commercially available stationary phases, but these were unsuccessful." (Page 3, line 10-13 of the specification)

Further attempts to separate the stereoisomers involved forming the methyl ester of mixtures of the stereoisomers (see Example 1) and then separating the stereoisomers of the methyl esters. Even using the methyl esters, as described in the specification, "[m]any attempts at separation were carried out on the two mixtures of esters produced in Example 1 below, using chiral HPLC on a variety of commercially available stationary phases and mobile phases, but at best this method was successful on an analytical level and separation was not possible on a preparative scale." (Page 3, line 15 through page 4 line 3 of the specification)
The inventors were finally able to separate the stereoisomers as described in Example 2. Once the methyl esters were separated they still had to be converted back into the acids to yield the purified stereoisomers of the present invention.

Enantiomer is not anticipated or made obvious by racemate

The Federal Circuit decision in Forest Laboratories Inc. v. Ivax Pharmaceuticals Inc., 84 USPQ2d 1099 (Fed. Cir. 2007) (Forest), is relevant to the examiners contention that Nials either anticipates or in the alternate renders obvious claims 9, 17, and 19-21.

One matter at issue in Forest was whether or not a reference, [Smith] which disclosed racemic citalopram, anticipated a "substantially pure' (+)-citalopram." The court found that the racemate did not anticipate the enantiomer because Smith did not disclose or enable the enantiomer.

Further in Forest, the court notes that "[t]he Smith reference is a pharmacology paper, and not a chemical paper." And further notes that it "does not enable the preparation of the (+) enantiomer of citalopram." Based on these statements the court concluded that (+)-citalopram is not anticipated by Smith.

The court in Forest found that racemate disclosed in Smith did not make obvious the. enantiomer. In concluding that the enantiomer was not obvious, the court discusses that the

evidence indicated that the enantiomers of citalopram would have been difficult for a person of ordinary skill in the art to separate.

The facts of the Forest case parallel those of the present invention. As discussed above the separation of the stereoisomers claimed in the present application was not routine but required steps in addition to simple chiral HPLC separation. Nials is a pharmacology paper, and contains no teaching of how to separate the stereoisomers. As such, Nials does not provide one with possession of the separated isomers; it is the disclosure of the present application that places the purified stereoisomers in the hands of a skilled artisan.

Thus, as supported by the arguments above and precedential case law, the stereoisomers of the present invention are not obvious in view of Nials. Therefore the Applicants request the withdrawal of the rejection under 35 USC §103.

Conclusion

Applicants submit that all of the pending claims 9, 10, 16, 17 and 19-28, as amended, are patentable. Applicants request reconsideration, withdrawal of the rejections, and allowance of the application. The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

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/Cynthia M. Bott/

Cynthia M. Bott,
Reg. No. 46,568
Attorney for Applicants

BRINKS HOFER GILSON & LIONE
524 South Main Street
Suite 200
Ann Arbor, Michigan 48104-2921
(734) 302-6046

CMB/dms